CALIFORNIA DEPARTMENT OF FOOD AND AGRICULTURE
MEDICAL TOXICOLOGY BRANCH
SUMMARY OF TOXICOLOGY DATA

HEPTACHLOR

SB 950-068 , Tolerance #104

July 31, 1986
Revised November 13, 1986

I. DATA GAP STATUS

Chronic rat: Data gap; Inadequate study; Possible adverse effect indicated

Chronic dog: Data gap; No study

Chronic mouse: Data gap; Inadequate study; Possible adverse effect indicated

Onco rat: Data gap; Inadequate study; Possible adverse effect indicated

Onco mouse: Data gap; Inadequate study; Possible adverse effect indicated

Comb rat: Data gap; Inadequate study; Possible adverse effect indicated

Repro rat: Data gap; Inadequate study; Possible adverse effect indicated

Terato rat: Data gap; No study

Terato rabbit: Data gap; Inadequate study; No adverse effect indicated

Gene mutation: No data gap; No adverse effect

Chromosome: Data gap; Inadequate study; Possible adverse effect indicated

DNA damage: Data gap; Inadequate study; Possible adverse effect indicated

Neurotox: Not required

Note, Toxicology one-liners are attached

** indicates acceptable study
Bold face indicates possible adverse effect
File name 06B SB068HEP.BKD

II. TOXICOLOGY ONE LINERS

CHRONIC RAT

026 16947 (11/10/59, Kettering Lab) JR 5/24/85. One liner: 25 males and 25 females per group fed 0, 0.5, 2.5, 5.0, 7.5, or 10.0 ppm heptachlor epoxide for 108 weeks. Morphological changes in liver at all doses; increased liver weights, especially in females; decreased body weights, especially in males, 10 ppm; nephritis. Deficiencies--high dose too low; no rationale for dose selection; no analysis of dose solution; too few animals; missing tables.

CHRONIC DOG

Data gap; No studies submitted.

CHRONIC MOUSE

026 16951 (7/9/65) JR 5/23/85. One liner: 100 males and 100 females per group fed 0 or 10 ppm heptachlor and heptachlor epoxide for two years. Hepatic hyperplasia and benign hepatoma. Deficiencies--the submission is a summary with one summary table of neoplasms and no individual data.

EPA One liner: NOEL less than 10 ppm (only level tested). (increased hepatic hyperplasia; increased benign hepatoma).

CHRONIC VARIOUS SPECIES

025 16941 (84, Velsicol) JR 5/20/85. One liner: One paragraph review of subacute and chronic studies with heptachlor. No adverse effects noted. Too little information for assessment.

ONCOGENICITY GENERAL COMMENTS

These oncogenicity and combination studies are consistent with others (see 0206 16950 one-liner below) in showing liver tumor induction.

ONCO RAT

015 914002 (77, NCI/Gulf South Research Institute) JS 4/1/85. One liner: 10 males and 10 females as negative controls, 50 males fed 80 ppm, 50 males fed 160 ppm, 50 females fed 40 ppm, 50 females fed 80 ppm. Thyroid follicular

cell adenomas in females at high dose and males at mid dose. Deficiencies--changes in dose levels during study; only two dose levels per sex; insufficient controls; no hematology; no GLP; no individual data; no time to tumor.

ONCO MOUSE

015 914002 (77, NCI/Gulf South Research Institute) JS 4/1/85. One liner: 20 males and 10 females as negative controls, 50 males fed 10 ppm, 50 males fed 20 ppm, 50 females fed 20 ppm, 50 females fed 40 ppm. Hepatocarcinoma and nodular hyperplasia at high dose. Deficiencies--high mortality in males led to altered dose levels during study; only two dose levels per sex; too few control animals; no hematology; no individual data; no time to tumor.

ONCO MOUSE CONTINUED

028 16974 (84, Naylor Dana Institute) JR 5/21/85. One liner: Males treated with 20 ppm DEN for 14 weeks followed by 5 or 10 ppm technical heptachlor. Suggests heptachlor may be a promoter for DEN carcinogenesis in the liver. Deficiencies--males only; only 25 week exposure, not chronic; protocol difficult to follow.

016 31870 (9/26/73, IRDC) JR 9/6/85. One liner: 100 males and 100 females fed 0, 1.0, 5.0, 10.0 ppm of mixture of 75% heptachlor epoxide and 25% heptachlor in corn oil. Positive control 250 ppm 2-acetamidofluorene. Increased liver weight in both sexes at all dose levels; decreased late body weight gain in females at 10 ppm; hepatocytomegaly at all dose levels; nodular hyperplasia in livers. NOEL less than 1 ppm. Deficiencies--No rationale for dosage selection; no justification for mixture in test material; no analysis

of dose solution; no hematology; not all suggested tissues and organs examined by histopathology

ONCO MOUSE, RAT

0206 16950 (1976, Case Western Reserve University) JR 5/23/85. One liner: Review of carcinogenicity studies indicates liver tumor induction in both mice and rats. Because it is a review, there is too little detail to evaluate.

COMB RAT

026 16948 (8/17/55, Kettering Lab) JR 5/24/85. One liner: 20 males and 20 females per group fed 0, 1.5, 3.0, 5.0, 7.0, 10.0 ppm. Increased liver weights in males at 10.0 ppm and morphological changes of questionable significance in livers at 7.0 and 10.0 ppm. Deficiencies--test material not defined; too few animals; excessive mortality; no rationale for dosage selection; high dose is insufficient; method of dosing food unsatisfactory; reproduction part of study inadequate.

EPA One liner: NOEL = 5 ppm; LEL = 7 ppm. (liver cell swelling, homogeneity of cytoplasm and peripheral arrangement of cytoplasmic granules in the hepatic cells in the central zone of the lobules). Levels tested = 1.5 to 10 ppm.

COMB MOUSE

004, 007, 008, 009, 010, 013 (1977, RPAR statements) JS 3/28/85. One liner: RPAR statements indicate hepatocellular carcinoma in mice (Vol 004).

REPRO RAT

027 16967 (Inst. Industrial Hygiene & Occupational Med., Czechoslovakia) JR 5/24/85. One liner: Brief publication of one generation, two litters given 6 mg/kg of 98.1% heptachlor. Increased pup mortality and decreased mean litter size; cataract formation in eyes. Deficiencies--too little information.

027 16968 (2/27/67, Kettering Lab) JR 5/24/85. One liner: 20 males and 40 females as negative controls, 10 males and 20 females per group fed 0.3, 3, or 7 ppm mixture of heptachlor and heptachlor epoxide. No adverse effects indicated. Deficiencies--dosing only three weeks; high dose too low; necropsy and histopathology not done on parents or first generation offspring; excessive mortality; data presented only in summary tables with no individual data given. Unacceptable.

EPA One liner: Reproductive NOEL greater than 7 ppm (highest level tested). Levels tested = 0.3, 3, 7 ppm.

025 16938 (1984, Velsicol) JR 5/20/85. One liner: One paragraph summary of a three generation study. No adverse effects noted. Insufficient information for assessment.

TERATO RAT

Data gap; No study submitted.

TERATO RABBIT

027 16969 (3/21/69, Int'l Research & Development Corp.) JR 5/24/85. One liner: 22 females as negative controls and 20 females given 5 mg/kg/day by oral gavage. No adverse effects indicated. Deficiencies--heptachlor epoxide instead of heptachlor; one dose only with no rationale for the level; no maternal toxicity; dosing only on days 6-11; no report of detailed examination of soft tissues; no individual data. Unacceptable. Can't be upgraded.

025 16939 (1984, Velsicol) JR 5/20/85. One liner: One paragraph summary of teratogenic study. No adverse effects noted. Insufficient information for assessment.

**GENE MUTATION

**Overall evaluation of gene mutation studies (11/13/86):

Although none of the submitted studies is individually acceptable, they along with the review by D.J. Brusick (104-016 31873 and 104-018 46802) present a consistent pattern of no gene mutation induction by heptachlor. Therefore the data gap is filled since there are sufficient data to assess this aspect of mutagenicity.

General Comment (7/31/86): The cover letter for the Velsicol Chemical Corporation submission 104-017 on mutagenicity assays for heptachlor, dated 3/27/86 makes several points. 1. There is resubmission of the National Toxicology Program Ames assay results, with additional information. These have been reviewed together--see the following summary and the more detailed Supplemental Information Review Worksheet. Although the letter argues that

these studies follow well-established procedures, the need for a specific protocol for any given study is evident from the fact that the additional information specifies triplicate plates for each strain and retesting to confirm the results, neither of which was done in this particular study. 2. There is a request for reconsideration of the Ames assay report of K. Maruyama. The principle that the total available information should be considered, even though the individual studies may be incomplete is not at issue here. The initial review criticized the study only for not testing all four strains and not having a confirming repeat assay. If other studies are submitted, which complement and complete this study, they will be reviewed in that light. 3. There is resubmission of the mouse dominant lethal study with additional information. These have been reviewed together--see the following summary and the more detailed Supplemental Information Review Worksheet. 4. Chromosome aberration and sister chromatid exchange results are anticipated.

104-018 46802 Supplement to review by D.J. Brusick, 6/86. BKD 11/13/86. Heptachlor mutagenesis assays of all three (842, 843, 844) types are reviewed. Gene mutation assays in bacteria, yeast, Drosophila, and mammalian cells are consistently negative. The one positive result among three DNA mutagenesis assays is not considered compelling by the author. This supplement discusses the recent SCE study (CDFA volume 104-018, 46801) and recent chromosome aberration study (CDFA volume 104-108, 46800), both of which are positive.

104-018 46799 (Supplement to 104-017 43587 and 104-016 31875), Gene mutation, Ames, 842, (Microbiological Associates or SRI International, 1/83) BKD 11/10/86. Heptachlor. Salmonella strains TA98, TA100, TA1535, TA1537. 0, 0.1, 0.3, 1.0, 3.3, 10.0, 33.0 ug/plate without activation; 0, 100.0, 333.0, 1000.0, 3333.0, 10000.0 ug/plate with activation. No adverse effects. Incomplete Unacceptable. Summary data with general protocol which is too

brief and is at variance with the actual assay, no description of test material, no confirmatory assay.

016 31874 (8/80, Chemicals Inspection & Testing Institute, Japan) JR 9/6/85. One liner: 0, 10, 50, 100, 500, 1000, 5000 ug/plate, duplicate plates at each level. 2-AA and AF-2 as positive controls. No adverse effects. Deficiencies--only two strains tested; no repeat experiment.
EPA One liner: Negative mutagen. Negative on histidine-deficient strains of Salmonella typhimurium TA 98 and TA 100. Acceptable.

026 16961 (University of Kentucky) JR 5/22/85. One liner: Ames assay of several pesticides including a mixture of heptachlor and heptachlor epoxide. No adverse effect noted. Insufficient information for assessment.

026 16959 (76) JR 5/22/85. One liner: Journal article screening pesticides, including heptachlor, with Bacillus subtilis, Escherichia coli, and Salmonella typhimurium for gene mutations. No adverse effect noted. Insufficient information for assessment.

GENE MUTATION

025 16940 (1984, Velsicol) JR 5/20/85. One liner: This section and parts of the accompanying Part III of the same submission (122-025), review the literature on mutagenicity assays of heptachlor. No adverse effect noted. Since the purpose is review, there is too little detail for assessment.

CHROMOSOME

017 43589 and 016 31876 (10/28/71 and 77, Industrial Bio-Test Laboratories, Inc.) BKD 7/31/86 and JR 9/6/85. One liner: Dominant lethal

assay in the mouse with 0, 7.5, or 15.0 mg/kg of mixture containing technical Heptachlor. No adverse effects. Deficiencies--source, purity, and stability of sample test material unstated; no individual data presented; statistical methods for evaluating homogeneity of groups and for comparing test and control group results are unstated; too few males; no quality assurance or sign off sheet; dose range finding results ambiguous; no positive controls.

EPA One liner: NOEL = 15 mg/kg (highest level tested).

104-018 46801 (Litton Bionetics, Inc., 4/2/86) BKD 11/12/86. In vitro chromosome aberrations (843). Heptachlor administered to Chinese hamster ovary cells at 0.000, 25.000, 30.000, 35.000, or 40.000 ug/ml with and without activation. Increased chromosome aberration frequencies at all doses with activation. Possible adverse effect. Incomplete Unacceptable. Duplicate cultures not done; insufficient information about test material, cell culture methods, cytotoxicity, S9 preparation, statistical results, and GLP.

DNA DAMAGE

104-018 46800 (Litton Bionetics, Inc., 4/2/86) BKD 11/12/86. In vitro sister chromatid exchange (843 or 844). Heptachlor administered to Chinese hamster ovary cells at 0.000, 0.830, 2.500, or 8.330 ug/ml in the first trial without activation, 0.000, 12.500, 15.000, 20.000, or 25.000 ug/ml in the second trial without activation, and 0.000, 2.500, 8.300, or 25.000 ug/ml in a single trial with activation. Increased sister chromatid exchange frequencies in all trials. Possible adverse effect. Incomplete Unacceptable. Duplicate cultures not done; insufficient information about test material, cell culture methods, cytotoxicity, S9 preparation, statistical results, and GLP.

NEUROTOXICOLOGY